

THE FOOD & DRUG LETTER®

Biweekly, in-depth analysis of regulations and issues affecting the drug and biologics industries

June 7, 2002

Issue No. 653

SCHERING-PLOUGH GMP CONSENT DECREE PUTS DRUG INDUSTRY ON NOTICE

In case the message wasn't already clear, take note: The FDA is serious about current good manufacturing practices (GMPs). The record \$500 million "disgorgement" of Schering-Plough, part of a consent decree signed May 22, was intended to fire a shot across the bow of the pharmaceutical industry.

"The agency has allowed itself to get into this situation of issuing warning letter after warning letter to the same company, without taking any action," said Eric Blumberg, the FDA's deputy chief counsel for litigation, who signed the decree. "The FDA has tried to send the message out that that's not going to happen anymore." Can more such enforcement action be expected in coming months? "When appropriate cases present themselves, absolutely yes," said Blumberg.

Schering's groundbreaking consent decree "has a tremendous impact beyond pharmaceutical companies to the whole FDA-regulated industry," said Suzan Onel, former FDA general counsel, now representing pharma clients with the firm of Kirkpatrick & Lockhart in Washington, D.C. "It's clear that the FDA has made GMP regulations their focus," said Onel. "The ante has been upped."

The agency may be prepared to take it up yet another notch. Although the consent decree has been signed by the court, funds have been earmarked to pay for the penalty and an action plan is being implemented to ensure GMP compliance, Schering may not be out of the woods yet. The company now faces an FDA criminal investigation, a development intended to hold individual Schering-Plough executives responsible for GMP shortcomings. According to FDA sources and industry observers, if an investigation comes to fruition it would be the first time the agency has pursued criminal sanctions for GMP violations against a major pharmaceutical company.

Same Stick, New Carrot

The trend toward more aggressive GMP enforcement is a sharp departure from the FDA's inspection and enforcement activities in the past. By federal law, the FDA is required to inspect all domestic and foreign pharmaceutical manufacturing and processing facilities. It isn't possible to inspect every FDA-regulated site, given the number of field agents available for the task.

If deviations from current GMP standards are noted during a plant visit, the inspector fills out a FDA 483 form, known as an Inspectional Observation report, which details deficiencies and is given to the company at the conclusion of the inspection. Last year, the agency issued 47 FDA 483 reports.

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Once a 483 report has been filed, a drug company can respond in writing, by either disputing the FDA's findings with supporting data or informing the agency how the company will comply with the regulation. In cases where GMP violations are deemed to pose a risk to the public, the agency may issue an untitled or warning letter to bring the infractions to the attention of a company's top management. A company that receives a letter typically has 15 days to respond and address the FDA's concerns. In turn, the agency may respond in writing, triggering another round of correspondence.

"The letters go back and forth for months or years," said Onel. "Typically, there are a great number of dialogues that go back and forth, discussions to forestall going to court."

Notices of violations are easy to ignore because the FDA lacks authority to impose civil monetary penalties. In extreme cases where the public health is at imminent risk of harm, the agency is empowered to shut down a production factory, seize shipments of product or take other action, but has no legal mechanism to issue fines for violations.

Calculated Decision

"The FDA has absolutely no authority to fine companies, zero," said pharmaceutical industry critic Sydney Wolfe, director of Public Citizen's Health Research Group, Washington, D.C. "They send you a warning letter, and you either clean it up or you don't. And if you don't clean it up, you don't lose a nickel."

In the pursuit to please stockholders and maintain the health of the bottom line, pharmaceutical company executives tend to allocate resources into areas that generate a higher return such as research or marketing. Paying fines and penalties is often perceived as "a cost of doing business," said Wolfe. "It's cheaper to do that than to put in good quality control and hire good managers."

This view is shared by those within the FDA as well. "Companies can count on the FDA to keep issuing inspection reports and warning letters," said Blumberg. "Some companies seem to sit back and

wait for the FDA to catch up to them. I have no facts to support it, but in my opinion, these companies appear to be making a calculated decision."

Pharmaceutical companies are quickly learning that a sanguine attitude about inspection reports and warning letters is a costly mistake. Under the new enforcement environment, firms in violation are likely to see regulatory action sooner – and more definitively applied.

In the spring of 2002, the FDA enacted a significant change in policy. From now on, all warning letters from the Drug Center are reviewed by the FDA's general counsel office before being issued. The FDA's general counsel tends to take a less charitable view toward violations. "We're frequently telling the districts of the center, no warning letter; take a case [to litigation] or forget it," said Blumberg. "No more huffing and puffing."

The number of warning and untitled letters issued by the FDA to drug companies for GMP violations has dropped dramatically in recent years, from 45 in 1995 to 15 in 2001.

As warning letters decrease in frequency, the FDA is making its enforcement efforts carry more weight. Having warning letters reviewed by the general counsel's office "is an attempt for [warning letters] to go down in number, but make the ones that are issued have more teeth to them," Onel said. "The agency has stated its intentions to get warning letters back to the level to where they are respected and responded to seriously by industry."

Disgorging Profits

Disgorgement of profits, established in a 1999 court ruling in the FDA's case against Abbott, is the agency's latest GMP enforcement weapon. Disgorgement is a sanction based on the premise that an individual or corporation is not entitled to profits gained by illegal means.

"Disgorgement is a strategy that the Federal Trade Commission has used for years and is quite effective," said Onel.

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Disgorgement is not a punitive measure, but meant as a deterrent by taking away profits to which a company, in the FDA's opinion, is not entitled. Unlike restitution, which is paid to a victim, disgorged funds are paid to the government.

The \$100 million penalty levied against Abbott was intended "to be large enough to attract industry's attention to an issue FDA was trying to address, and to serve as a meaningful deterrent," according to Blumberg.

Disgorgement is not meant to take away all profits generated by products in violation of the Food, Drug and Cosmetic (FD&C) Act – which, in the case of Schering-Plough, could have amounted to billions of dollars – but should be sufficiently severe to dissuade repeat behavior.

"The sums obtained in these decrees are not meant to be a complete disgorgement of all profits, only of those products in violation," explained Blumberg. "And even with respect to those products, FDA has not sought – to date – 100 percent disgorgement."

In light of the Schering case, the addition of disgorgement to the FDA's enforcement toolkit means it is "something we're likely to see more of in the months to come, especially for GMP issues," Onel said.

The pattern of the FDA's GMP enforcement may be an important signal to the industries it regulates, Onel suggests. The FDA "hit the medical device industry, and now they're in the pharmaceutical industry," she said. "They're crossing industries, so that could be a way to get everybody to wake up and pay attention."

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SCHERING-PLOUGH RESPONDS TO GMP DEFICIENCIES

Schering-Plough has implemented changes to address deficiencies in good manufacturing practices (GMPs). Some steps began long before entering the consent decree in May. Whether the company did enough, soon enough, may be debated.

- On May 1, 2001, the company submitted a GMP work plan to the FDA "designed to take a broad, systematic approach to all aspects of manufacturing and serve as a blueprint for quality and compliance initiatives."
- Among the organizational changes at the company was the formation of a Worldwide Quality Operations unit with the authority and independence to address quality issues throughout the company, to which quality personnel at FDA-regulated sites directly report.
- Schering committed to spending \$50 million in new equipment, process and systems improvement.
- The company formed a GMP review board, which included three prominent former FDA officials, to oversee progress in the company's compliance efforts and reporting to the FDA.
- Staff and consultants were hired to requalify and revalidate equipment and processes.
- Schering-Plough President and Chief Operating Officer Raul Cesan resigned, effective July 15, 2001.
- The company plans to hire 500 people to strengthen quality and production.
- By the end of 2002, the company expects to have increased its "authorized quality-related positions" at FDA-regulated sites by 30 percent over 1999 levels.

The company realizes that it must work to restore the faith of customers and stockholders – as well as FDA officials – and that it is now on the right GMP track. "We've gone a long way toward restoring FDA's confidence in our GMP compliance," said Schering spokesperson Bob Consalvo. "We've received product approvals over this period of time, our plans remain open, our products are on the market. We've worked out the steps we need to take to enhance and improve compliance."

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According to the FDA's complaint against Schering-Plough, which provided the basis for the subsequent consent decree, the company had a history of failing to comply with GMP requirements during the manufacture of drugs at its facilities located in New Jersey and Puerto Rico.

The government's action followed 13 inspections since 1998 at four facilities in New Jersey where FDA inspectors found "significant violations [of GMP] regulations related to facilities, manufacturing, quality assurance, equipment, laboratories and labeling," according to the agency.

The facilities in question produce about 125 different prescription and over-the-counter drugs, representing about 90 percent of the company's drug products.

On March 1, 2001, Public Citizen's Health Research Group sent a letter to Health and Human Services (HHS) Secretary Tommy Thompson requesting that the department, which oversees the FDA, investigate Schering-Plough for allegedly shipping asthma drug inhalers that may not have contained the active ingredient.

"If you knowingly ship out products without active ingredient, as we believe they did, that is raised to the level of a criminal violation," said Wolfe, whose group was leaked an embarrassing audit of Schering-Plough conducted by an outside consultant.

Schering-Plough had experienced chronic problems in the manufacture of its albuterol inhaler products, which are used by patients with asthma. In September 1999, albuterol manufacturing problems led the company to issue a recall of more than 190,000 inhaler canisters because some did not contain the active ingredient. A second recall, involving almost 60 million canisters, was announced March 29, 2000.

Subsequently, Aug. 9, 2001, Health Research Group followed up with another letter to Thompson that claimed an analysis of adverse reaction report data revealed "a pattern of death in users of Schering-Plough albuterol products" that clustered around the

1999-2000 time period of the two product recalls. According to the group, there were a total of 17 deaths for which the Schering-Plough albuterol was listed as the "primary suspect" between the fourth quarter of 1998 and the second quarter of 2000. Of the 17 patients with known dates of death, 10 were using, or attempting to use, inhalers from the lots which were eventually recalled, according to Wolfe.

Schering-Plough quickly issued a rebuttal, claiming that Health Research Group "misrepresented data and drew unfounded conclusions, which could unnecessarily alarm asthma patients." The company said that it "knows of no death or injury to a patient ... caused by an inhaler lacking active ingredient," and is vigorously contesting lawsuits claiming to the contrary.

"[I]n all adverse event reports involving deaths where an albuterol canister was tested by the company, the canister was shown to contain active ingredient," according to the firm. "Further, every inhaler involved in a patient's claim of injury that has been tested by the company has been shown to date to contain active ingredient."

The Health Research Group's allegations "are based on a flawed analysis of a small number of events, which does not address event rates that occur with similar asthma rescue inhaler products," the company said.

As public relations, the revelations couldn't have helped Schering-Plough's situation. With several important drugs off patent and others approaching the end of their product cycle, it was important that the company kept its pipeline open. The agency was contemplating approval of Peg-Intron (peginterferon alfa-2b), which in combination with Rebetol (ribavirin) is for the treatment of chronic hepatitis C infection.

Also, an FDA advisory panel was about to sit in judgment of Schering's Clarinex (desloratadine), the once-daily successor to Claritin (loratadine) for the treatment of seasonal allergic rhinitis.

The FDA sent Schering-Plough an "approvable" letter for Clarinex Jan. 25, 2001, that was predicated

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on improving GMP compliance at its production facilities. "One of the conditions of approval was the resolution of manufacturing issues," said Consalvo.

Approval for Clarinex was granted by the FDA Dec. 21, 2001.

A commitment to GMP compliance is central to the consent decree entered by Schering-Plough May 17. Among the steps required of the company is the implementation of a work plan to address GMP deficiencies. Schering-Plough will retain qualified outside experts to determine that manufacturing methods, procedures and controls at the company's production facilities comply with current GMP requirements.

Schering will pay the record \$500 million disgorgement in two equal installments of \$250 million, with the first one paid in the second quarter of 2002 and the balance in the second quarter of 2003. If actions are not completed on time, the consent decree includes provisions for a penalty of \$15,000 a day for every deadline missed, up to \$50 million a year. In addition, a royalty payment of 24.6 percent of net U.S. sales can be imposed for every product that has not been revalidated on time.

Aside from the record \$500 million disgorgement, the decree also requires the company to pay \$471,500 to cover the cost of inspections conducted by the company since 1998.

Post-decree Company

Schering-Plough's GMP settlement will affect changes throughout the company. "Under the consent decree, we are essentially revalidating and certifying each of the products we will continue to produce and market," explained Consalvo. The company is scheduled to complete its revalidation plans by the end of 2005.

In addition, Schering-Plough is temporarily suspending pro-

duction of certain products at its Manati, Puerto Rico, site while GMP programs are implemented, mainly affecting veterinary medicine products that together generated \$50 million in sales for the company in 2001.

The consent decree includes a recall of all lots of theophylline and Proventil (albuterol sulfate) tablets and syrup, which have been discontinued in the U.S. market. Albuterol inhalers are not affected by the recall. Theophylline and the Proventil line, which generated annual sales of about \$45 million, "make up a very small percentage of the albuterol market share," said Consalvo. "The inhalers and the solution for inhalation are the vast majority of patient use of that product."

Dozens of Schering-Plough over-the-counter (OTC) and prescription drug products are being discontinued under the consent decree, including some versions of griseofulvin, Gyne-Lotrimin, garamycin and trilafon/perphenazine tablets.

The discontinued goods are "mostly older products on the prescription side, products that we no longer promote or detail," said Consalvo. "On the OTC side, many of these are different presentations of products, line extensions. Some of them have not been on the market for a while anyway and weren't available."

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Most Common GMP Issues Cited by FDA

- Process validation
 - Equipment qualification
 - Lack of validation of analytical methods
 - *Ad hoc* manufacturing changes without quality control approval
 - Lack of written protocols for standard operating procedures (SOPs) and manufacturing processes; inadequate change control
- Invalidating out-of-specification (OOS) test results without justification
- Laboratory
 - Analysts not adequately trained
 - Failure to document all tests performed
- Sterile processing
 - Environmental controls excursion
 - Use of older equipment
 - Media fill failures

Source: FDA

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The cumulative impact of the consent decree is expected to impact Schering-Plough's bottom line. In May, the company lowered its earnings projection for 2002, a mid-single-digit percentage increase in earnings per share rather than the low-double-digit percentage increase that had been previously projected.

Individual Responsibility

By naming individuals as defendants in enforcement actions, the FDA wants to drive home the point that executives are responsible for the actions of the corporations that they manage.

"Individual responsibility has always been a centerpiece of the agency's enforcement," explained Blumberg. "We have always insisted that responsible individuals be held accountable for what their corporations do."

In cases where companies have received repeated notices and warnings, executives often react with surprise and anger at being personally identified in a court proceeding, he said.

"I wish corporate leaders who are making decisions about whether to spend money on GMP compliance would call officials at Abbott and Schering-Plough and Wyeth and find out what it's like to be named in one of these consent decrees," said Blumberg. "It doesn't seem to be one of the factors leaders take into account when they're making decisions not to spend the money [on GMP]. Yet when it's time to put their name down as a defendant, they argue and whine about the unfairness of it all. They just don't connect the dots. If they don't want their peers and friends to know about their involvement in a consent decree, or have to explain it to their children, they should think about that now, not when they get a 50-page 483 [GMP compliance report]."

It appears that individual responsibility may extend to possible criminal sanctions. The FDA's Office of Criminal Investigations has begun an inquiry into GMP practices at Schering-Plough. The investigation is presently "in its formative stage," accord-

ing to a high-ranking agency official who declined to be identified.

In its 10-Q quarterly report filed with the U.S. Securities and Exchange Commission May 15, Schering-Plough discreetly mentioned that the company is the target of a criminal investigation by the FDA.

"We've been advised by FDA's Office of Criminal Investigations in Puerto Rico that they are conducting an investigation that might focus on one or more of our products," said Consalvo. "The investigation is in a very preliminary stage, and that's all we know at this point. We don't know what products or sites are involved."

Although Health Research Group urged HHS to launch a criminal investigation into asthma inhalers, Consalvo pointed out that the inhalers in question are manufactured at Schering's Kenilworth, N.J., plant and not in Puerto Rico.

"We don't have any indication that there's an investigation regarding the Public Citizen allegations about aerosol inhalers," said Consalvo, who declined to comment further on the group's charges.

Ripple Effects

The Schering-Plough consent decree is sending repercussions throughout the pharmaceutical industry. In this regulatory environment, companies are less likely to get a pass for GMP violations as they may have done in the past.

"Clearly, all companies need to take GMPs and standard operating procedures (SOPs) seriously," said Onel. "They need to be sure to have procedures in place to make sure they can audit and verify and validate what's going on."

Compliance with GMPs starts at the top of a pharmaceutical company. If upper management is blasé toward GMP compliance, the mind-set will drift down throughout the ranks of a company, said pharmaceutical compliance consultant Michael Beckloff of Overland Park, Kan.

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“GMPs start with attitudes and opinions of upper management,” he said. “If management supports GMP compliance, you can expect a trickle-down effect. Schering-Plough apparently didn’t think GMPs were important or apply to their operation. Once that takes root, it takes forever to change that thinking.”

Indeed, according to the report of an internal audit performed for Schering, obtained and released by Health Research Group, line personnel didn’t feel that the company valued GMP compliance and quality as highly as other priorities such as maintaining production.

“Most managers/supervisors have adopted a wait and see attitude, to determine if upper management will ‘walk the walk’ with respect to long-term commitment to product quality,” the consulting firm wrote in its 2000 report. “They state that for many years, they have been under significant pressure to get production out and don’t feel they have enough time or people to do a quality job. They indicated that there has been in the past a continual push for increased production and decreased downtime sometimes at the expense of high-quality work and GMP compliance. They believe there has been an imbalance between quality and production, leaning considerably toward the side of production.”

A Systems Approach

The FDA regards current good manufacturing practices (GMPs) in terms of six systems:

1. Quality System
2. Facilities and Equipment System
3. Materials System
4. Production System
5. Packaging and Labeling System
6. Laboratory Control System

According to the agency’s philosophy, a “state of control” is required to produce finished drug products for which there is adequate level of assurance of quality, strength and purity. If any of the six systems is out of control, i.e., fails to meet GMP standards, the entire company is considered out of control.

Source: FDA

The FDA intends to use the tools of enforcement at its disposal to tip the scale back in the other direction. “We want company leaders to take GMP seriously, and factor it in to their decisions,” said Blumberg. “Changing corporate culture is very hard. Even if the guys at the top get it, making people change the way they’re accustomed to doing business is very difficult.”

FDA, ABBOTT SETTING THE STAGE FOR SCHERING

The die for the Schering-Plough case was cast in 1999, when the FDA sought to teach Abbott the consequences of GMP violations. After years of persistent problems at an Abbott facility that manufactures in vitro diagnostic devices, the FDA filed a consent decree with the U.S. District Court in Northern Illinois Nov. 2.

According to the FDA, an establishment inspection conducted between May and July 1999 revealed 45 deviations from quality control standards. Some of the violations dated back to 1993. Over the years, Abbott and the FDA met no fewer than 10 times to discuss current GMPs. Beginning in 1995, the agency allowed the company to continue operating under an FDA-monitored compliance plan. In early 1998, the FDA terminated the plan because, “in its view, the company was not making sufficient progress,” according to Blumberg.

The 1999 consent decree with Abbott was unusual for three reasons, the most obvious being a “disgorgement” of profits in the form of a one-time payment of \$100 million to the U.S. Treasury. Under the terms of the consent decree, Abbott is also required to validate manufacturing and quality processes or pay \$15,000 per business day for each process and system not validated. Another provision required Abbott to pay 16 percent of gross revenues generated by the sale of any “medically necessary” product that is not validated within a year.

The FDA had never successfully sought disgorgement before, a strategy used by other federal agencies to separate a corporation from profits to

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Selected FDA GMP Warning and Untitled Letters Issued 2000-2002

Date	Company	FDA District	Issues
9/19/01	Cardinal Laboratories	Los Angeles	Testing, written procedures, equipment maintenance, laboratory controls, record-keeping at Azusa, Calif., facility
9/18/01	Pharmacia & Upjohn	San Juan	Sterility, failure to submit reports at Arecibo, Puerto Rico, facility
2/22/02	AstraZeneca	Philadelphia	Quality control at facility in Newark, Del.
11/9/01	Accumed	New Jersey	Investigation of out-of-specification (OOS) results, labeling, validation of equipment and processes
11/2/01	Baxter Healthcare	Chicago	Laboratory controls at Round Lake, Ill., facility
11/9/01	Purdue Pharma	New Jersey	Quality control at facility in Totowa, N.J.
10/12/01	American Pharmaceutical Partners	Chicago	Investigating OOS results at facility in Melrose Park, Ill.
1/14/02	Bachem California	Los Angeles	Decontamination, maintenance, production and process controls at Torrance, Calif., plant
6/24/01	Bayer	Biologics Center	Investigating OOS results, sterility, written procedures for production and process controls at facility in Clayton, N.C., facility
7/12/01	Boehringer Ingelheim	Cincinnati	Laboratory controls, written procedures for production and process controls, environmental conditions, validation of systems at plant in Columbus, Ohio
10/15/01	Burnham Laboratories	Chicago	Quality control, equipment cleaning and maintenance, validation of systems
12/7/01	Cardinal Enterprises	New England	Record-keeping, sterility
7/10/01	Cardinal Health	Cincinnati	Records, validation
6/28/01	FIDA	Drug Center	Quality controls, validation issues at facility in Padova, Italy
10/2/01	Northeast General	Drug Center	Pharmaceutical factory quality controls at plant in Shenyang, China
3/17/02	Pharmacia	San Juan	Quality control, contamination at facility in Caguas, Puerto Rico
6/18/01	Salsbury Chemicals	Kansas City	Quality control, written procedures
9/5/01	Syncor International		Quality control, written procedures, record-keeping
9/27/01	Unilever	Chicago	Environmental issues, laboratory methods, record-keeping at plant in Chicago
11/11/01	Pharmacia	Drug Center	Validation of systems and controls, documentation at facilities in Sweden
9/19/00	Glaxo Wellcome	Drug Center	Sterility at facility in Verona, Italy
2/3/00	Pharmacia & Upjohn	Drug Center	Sterility, record-keeping at facility in Nerviano, Italy

INDUSTRY SEEKING CLARITY IN GMP GUIDELINES

Some in the industry contend that good manufacturing practice (GMP) guidelines used by the FDA are vague and ambiguous, leading to different interpretations that force pharmaceutical companies to second-guess what the agency wants.

GMP guidelines are written as performance standards, giving companies latitude to determine how they can most efficiently and economically meet the objective.

“GMPs are regulations that are open to interpretation,” said attorney Suzan Onel, of Kirkpatrick & Lockhart in Washington, D.C. “Usually there are two sides to the issue, with the FDA saying certain things aren’t being done.”

The pharmaceutical industry is stymied by “the paucity of guidelines and standards for good manufacturing practices,” said Jeff Trehwitt of Pharmaceutical Research and Manufacturers of America (PhRMA).

“There are very few technical guidelines on good manufacturing practices, and those that exist are outdated and don’t reflect production approaches at today’s plants,” Trehwitt said. “This lack of technical guidelines can easily lead to differing interpretations of GMP regulations among FDA inspectors as well as the industry.”

The confusion results in “a frustrating situation where companies basically have to resort to trying to interpret FDA expectations from publicly available GMP compliance citations and warning letters, instead of a review of consistent standards and guidelines,” he said.

PhRMA is “eager to partner with the FDA to develop and implement a consistent and transparent science-based process for regulating the manufacture of pharmaceutical products,” said Trehwitt.

Eric Blumberg, the FDA’s chief litigator, “emphatically disagrees” that GMP standards are ambiguous. “They are intentionally written with flexibility to

use words like ‘suitable,’ ‘adequate,’ and ‘sufficient,’” he said. “They must be written that way because they cover hundreds if not thousands of factual situations. We’re trying to give drug companies the flexibility to make products in any way they can as long as it’s scientifically supportable.”

“The idea that they’re so flexible that companies don’t understand it, I don’t buy it,” said Blumberg. “Nobody in the cases that we bring has ever said, ‘Your regulations are so ambiguous that we can’t comply with it.’ That’s not the defense we hear. First, if companies don’t have that [compliance] capability in-house, they’ve got a problem. Second, there are plenty of consulting firms out there who make a handsome livelihood out of telling these companies what is and what is not compliance with GMP. That’s not to say that there aren’t GMP issues that are not cutting-edge. However, if something is that questionable or ambiguous, FDA doesn’t bring a case on it. There may be GMP issues out there, but that’s not what these cases are about.”

Blumberg also rejects the argument that many GMP issues that attract the FDA’s attention are administrative details and paperwork that don’t affect the quality of products. “Enron was paperwork, too,” he said.

“Scientists write things down. They’re making drugs, not shoe polish,” he said. “Unless things are written down, scrupulously recorded, there’s no record for anybody inside or outside the company to check. This is an industry that makes its living on details. They’re making drugs that are shipped to scores of millions of people. If you make a mistake, it can be very serious.”

The FDA “is not bringing cases because somebody left off a second signature or failed to record some factoid,” Blumberg said. “These issues are much bigger than that.”

Pharmaceutical companies “seem to take a great deal of assurance because there are no bodies,” he said. “Nobody got hurt. That’s a notoriously unreliable way to evaluate whether your product is safe and effective. Unless there are acute injuries associated with your product, you’d never know.”

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which it is not entitled. Previously, courts had held that the Food, Drug and Cosmetic (FD&C) Act does not empower the FDA to impose an equitable remedy unless it is explicitly authorized by the statute. In the Abbott case, the U.S. Court of Appeals held in a Sept. 13, 1999, decision that the FDA is empowered to seek any remedy not expressly prohibited by the FD&C Act – including the extraction of undeserved profits.

Other pharmaceutical companies have entered consent decrees with the FDA to resolve GMP issues. The next major pharmaceutical company to get snared in GMP enforcement was American Home Products (AHP) division Wyeth-Ayerst, which entered into a consent decree with the FDA in October 2000 to settle repeated GMP violations at its facilities in Marietta, Pa., and Pearl River, N. Y., dating back to 1995.

Problems with manufacturing processes at Wyeth's Marietta plant, which produced influenza vaccine, led to its temporary closure. The interruption in production contributed to a nationwide delay in the availability of flu vaccine in time for the winter season.

The consent decree was sought because the company failed to correct GMP violations despite repeated FDA inspection reports, warning letters and the June 1999 seizure of hundreds of doses of prescription drugs and vaccine produced at one non-compliant facility.

Under terms of the consent decree, Wyeth-Ayerst was required to pay a \$30 million disgorgement and take specific steps to improve

GMP compliance, or pay \$15,000 per violation per day up to \$5 million.

"Thirty million dollars is substantial money to us, no doubt about that," Wyeth Senior Vice President Bruce Burlington told the press after the consent decree was signed. "It is clear that FDA did regard these problems as problems that needed more attention and at a faster pace than we achieved."

The consent decree required Wyeth-Ayerst to hire a consultant to perform a GMP inspection at the Marietta and Pearl River facilities. Any observations found during the inspection were to be addressed by the company within a specified time period, and then reinspected by a consultant. Expert consultants were to be hired to review Wyeth-Ayerst's quality assurance (QA) and quality control (QC) programs and management systems.

On May 3, 2002, the FDA filed a consent decree against Watson Pharmaceuticals, citing "numerous, recurring and significant violations of current good manufacturing practice requirements" at the company's manufacturing plant in Corona, Calif.

Twenty-six of Watson's 170 branded and generic products are made at the Corona plant, a solid dosage facility that produces the company's leading products: hydrocodone, acetaminophen and oral contraceptives.

Under the consent decree, Watson is required to hire an independent consultant to conduct inspections of their Corona facility at least once a year.



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